**Title: LIFE-BTK: Drug-Eluting Resorbable Scaffolds in 2024**

**Participants: Dr Sahil Parikh**

**Date: 26 Jan 2024**

**Dr Sahil Parikh**

"My name is Sahil Parikh. I'm an interventional cardiologist and an associate professor of medicine at Columbia University Irving Medical Centre in New York City. I am one of the co-principal investigators of the LIFE-BTK trial, along with Brian DeRubertis, also from New York, and Ramon Varcoe, from Sydney, Australia.

**Landscape for BTK Intervention at the Outset of LIFE-BTK**

We sort of use below-the-knee interventions as a synonym for chronic limb-threatening ischemia, or CLTI. So these were all patients with limb threat from severe arterial disease, many of which, many of these patients of which had significant below-the-knee artery disease, which had been plagued by technical problems, both with surgery and with endovascular techniques.

As a consequence, on the surgical side, distal bypass was probably the standard of care for these patients. And on an endovascular side, other than balloon angioplasty, no other technique had really been successfully shown in clinical trials to be superior to our old standby, which was balloon angioplasty.

And so in these patients, where the lesions are very complicated, they're long segments, they're often totally occluded, they're in the presence of other risk factors, like diabetes or kidney disease. Patients had a very difficult time when they had an intervention, keeping the intervention open. The phrase we use is patency.

The long-term patency of these patients generally was relatively poor, less than 50% at one year, which is a far cry from that which we see in other vascular circulations, for example, the femoral popliteal segment, just one level above, or certainly in the coronary arteries, which are similar in size, although the lesions tend to be much shorter.

So we have been seeking a better technology that can improve clinical outcomes and long-term patency for these patients for quite a while. And most of the techniques that we've used in these other areas to improve outcomes relate to drug delivery. So we have a mechanical scaffold or a mechanical intervention, like a balloon, that's coupled with a locally delivered drug that can prevent the restinosis cascade, which is the body's scar tissue response from causing re-occlusion of those vessels.

And none of those techniques had panned out, neither drug-coated balloons or other kinds of stents in a real-world population. So this was really where we started at the beginning of the LIFE-BTK trial, that it was surgery, angioplasty, plus or minus some other kind of treatment like atherectomy, which had never been shown to be superior to angioplasty, and a littered landscape of failed trials of stents, drug coated balloons and other technologies.

**Timeline of Resorbable Scaffold Technology**

Bioresorbable scaffolds have been sort of science fiction for the last two decades. As soon as stents became a mainstream technology for coronary artery or disease, there were engineers trying to develop bioresorbable scaffolds that were made of similar polymers that had physical properties that mimic a metallic stent with respect to radial strength and so on, that also allowed to have drug delivered locally to prevent restenosis.

And various polymers were experimented with and in the coronary circulation. About a decade ago, after a rigorous series of trials, a bioresorbable scaffold was first introduced by Abbott for clinical application globally. And it was at that time that vascular interventionalists, who, I think, out of both necessity and jealousy, started applying these devices off-label.

Many of us got our first flavour of their performance in the below-knee circulation at that time, using these so-called BRS devices off label for below-the-knee intervention. And at the time, the early results in those studies or series were very promising. And my partner in this trial, Ramon Varcoe, is one of the leaders in that space, and had studied patients over time out to five years, demonstrating superior primary efficacy and long-term patency in those patients.

And so that was sort of the genesis of the trial, and where the idea came from, if you will. Subsequently, the first-generation coronary device has actually been withdrawn from the market voluntarily, because it was not as resistant, thrombo-resistant, I should say, and perhaps not as successful as plain old metallic drug loading stents for coronary disease.

But nevertheless, there was always this fire inside that we wanted this for below-the-knee interventions, and that these circulations are different. And we needed something better than plain old balloon angioplasty, which is all we have now. And so in the coming decade, there were a number of iterations, the first of which was this spree BTK scaffold that was developed by Abbott as the next generation of their original bioresorbable scaffold.

It has a similar backbone, made out of a polymer that is both flexible and rigid at the same time, and is coated with another polymer that permits drug release, just like we would get from a coronary stent. It also has the advantage of being much thinner than the original device, which probably gives it favourable implantation characteristics.

And there are others. There are fast followers from other startups and strategic companies that are in a similar way, trying to develop polymeric resorbable scaffolds. And in fact, there are a handful of metallic resorbable scaffolds that rely on magnesium as the primary metal that are also in the pipeline. So the original proof of concept has now turned into a bit of a cottage industry of new scaffold technologies.

**Study Design, Patient Population and Inclusion Criteria of LIFE-BTK**

The LIFE-BTK trial was specifically a trial of below-the-knee interventions, which, as I've said, is synonymous with chronic limb-threatening ischemia. So we recruited 261 chronic limb-threatening ischemia patients from around the globe who had lesions in the infrapopliteal arteries that were up to 17 centimetres in length and had diameters of 2.5 to four millimetres.

And we randomised them two to one to receiving either the bioresorbable scaffold or plain old balloon angioplasty. And then we followed the patients for up to twelve months, looking for clinical and angiographic and or Doppler based endpoints that would suggest long-term patency. So the primary Composite endpoint was a composite of four things.

One was amputation of the index limb that was intervened upon. The others were related to patency, either avoidance of total occlusion or binary restenosis as adjudicated by Doppler. And then the final thing was a clinically driven target lesion revascularization. In other words, a repeat procedure, because a patient was either failing to heal or had recurrence of symptoms. And this four part composite was reported out at twelve months.

**Key Results and Safety Signals**

Yeah. So we were delighted to see that there was a significant improvement in the freedom from the composite endpoint that was, again, occlusion, binary restenosis, clinically driven target lesion revascularization or amputation of the ipsilateral limb.

In the drug-eluting reservable scaffold group, that group had a freedom of that composite endpoint of about 70 plus percent, compared to 40% in the control arm, which was plain old balloon angioplasty. The predominant components of this were the binary stenosis.

But also, even if we were to eliminate binary stenosis from the composite endpoint, there was significantly less amputation and also the need for repeat revascularization procedures or total occlusion in the target vessels. So we saw both clinically and patency-related significant benefit for the drug eluting reservoir scaffold.

**Considering These Results in Context of BASIL 2 and BEST-CLI**

It's been a busy couple of years in the space of critical limb ischemia treatment. I think the best CLI trial showed us that in patients who have adequate saphenous vein and who are fit for surgery, surgery is a great option for those patients and may result in superior outcomes.

Although in my clinical practice and in the majority of my colleagues practices, it was a small fraction of our patients who were actually BEST-CLI candidates. And in that context, I think BASIL 2 showed that if they have purely infrapopliteal disease, an endovascular strategy 1st may actually be superior. And I think that was with balloon angioplasty compared to surgery.

Now we have on top of that, a better endovascular technology. And I think life BTK will further amplify the benefits seen in BASIL 2, in which we've showed that angioplasty can be better than surgery in selected patients who had a below-the-knee disease.

Now we have a technology that can be both a supplement or a supplanting technology to angioplasty for below-the-knee treatment. So that's very exciting. It can potentially herald a new paradigm for treatment of these patients.

**Next Steps for the Use of this Technology**

Well, like any new technology, the device has to go through a rigorous regulatory process. The application for the device to be approved in the United States is with the FDA at present, and they'll, I'm sure, be deliberating over the data and other submitted articles from the sponsor, Abbott Vascular.

We are hopeful that we'll hear from the FDA about the role of this technology in the coming few quarters. So hopefully in the calendar year of 2024, but again, without the rigorous regulatory process, we won't be able to use this in patients. And I suspect the same predicate will apply globally in other parts of the world.

Chronic limb-threatening ischemia is an incredible global health epidemic that's been explosively increasing with diabetes as a public health hazard in this patient population especially, and that more treatments are still required for the treatment of these patients, and that the more our referring doctors and general practitioners are aware that these options exist, I think the better our chances are at saving limbs and saving lives in these otherwise very vulnerable patients.

And so I'm hopeful that in addition to LIFE-BTK, there are a number of other studies that are forthcoming that are hopefully going to use the LIFE-BTK paradigm of clinical trial design to generate level one evidence for new technologies for these patients. It's desperately needed.”